Amendments to the claims:

Claims 1-2 (Canceled)

3. (Currently Amended) A method for reducing mortality in a mammal with congestive heart failure, comprising administering to said mammal an effective amount **of the (R)-enantiomer** of N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (I).

Claim 4 (Canceled)

5. (New) A method for reducing mortality in a mammal with congestive heart failure, comprising administering to said mammal an effective amount of the (R)-enantiomer of N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (I), or a pharmaceutically acceptable salt thereof.

I. Status of the claims

Claims 3 and 5 are pending in this application. Claim 3 has been amended to incorporate the subject matter of canceled claim 4. The subject matter of claim 3 therefore involves administering the (R)-enantiomer of (I), as opposed to administering a racemic mixture of approximately equal amounts of enantiomers.

Claim 5 makes reference to administering (I) or pharmaceutically acceptable salts of (I). Support for the new claim appears in the specification in the Summary of the Invention on page 2 and at the bottom of page 4.

II. Claim Objection

The Examiner objected to claim 3 for being "incomplete." He suggested that the applicants amend claim 3 to specify that mortality is due to congestive heart failure.

Claim 3 recites a method for reducing mortality in a mammal with congestive heart failure, comprising administering to said mammal an effective amount of the (R)-enantiomer of N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (I). Applicants disagree that claim 3 is "incomplete." One skilled in the art would be able to determine whether "mortality" has been reduced or not in the recited group of patients on a therapeutic regimen. One skilled in the art can determine "mortality" in such a group of patients irrespective of the cause of the mortality. For at least this reason, the scope of the claim is clear and the objection should be withdrawn.

III. Claim Rejection under 35 U.S.C. § 103(a)

Claims 3-4 were rejected under 35 U.S.C. 103(a) as being obvious over Haikala et al. (U.S. RE38,102, "Haikala '102"), Haikala et al. (U.S. Patent No. 5,905,078; "Haikala et al. '078") or Applicants' acknowledgement at page 1, lines 2-4 of the third

paragraph of the specification, or Sircar (U.S. Patent No. 4,397,854) in view of Campbell (U.S. Patent No. 4,432,979) and Diamond et al. (U.S. Patent No. 4,517,310).

In support of the rejection, the Examiner cited Haikala '102, Haikala '078, applicants' specification, and Sircar as teaching administering N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (I) to patients to treat congestive heart failure. Acknowledging that Sircar does not "highlight" congestive heart failure per se, the Examiner cited Campbell and Diamond as teaching that cardiotonic agents are effective for the treatment of heart failure. The Examiner concluded that an effective treatment for congestive heart failure would logically decrease mortality.

Applicants respectfully traverse this rejection. As mentioned above, claim 3, the only independent claim now pending, recites a method for reducing mortality in a mammal with congestive heart failure, comprising administering to said mammal an effective amount of the (R)-enantiomer of N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (I). In order to establish a *prima facie* case of obviousness of this claim as well as claim 5, the Examiner must show, among other things, that one skilled in the art would have had a reasonable expectation of success in carrying out that method. *In re Dow Chem. Co.,* 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988); *see also* MPEP § 2143. As explained below, however, the cited references do not provide that showing.

As the Examiner mentioned, none of the cited references teach reducing the mortality of the patients receiving N-[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]acetamide (I). Congestive heart failure is a major medical problem. It is a progressive disease with a poor prognosis. There is an ongoing interest in the

role of positive inotropic (heart contractility enhancing) agents for treatment of congestive heart failure. However, the enthusiasm for positive inotropic therapy in congestive heart failure has been dampened by the results of clinical trials, which have shown that these drugs are associated with an increased risk of mortality. *See* page 1, lines 9-14, of the present application. Mortality reduction in congestive heart failure patients was therefore not an inherent or expected feature of positive inotropic agents as a class. To the contrary, the observed detrimental effect of certain positive inotropic agents on mortality has strongly limited the use of positive inotropic agents in the treatment of heart failure. This contradicts the Examiner's assumption that mortality would logically and necessarily have been expected to decrease upon administering of compound (I).

A number of published documents support the comments above. It is appropriate for applicants to refer to these other documents to illustrate that the references cited by the Examiner, when read in context of other documents, did not provide the necessary reasonable expectation of success to practice the claimed invention. *See, e.g., In re Dow chem. Co.,* 5 U.S.P.Q.2d at 1532.

It has been observed as reported in Kasper, "Fifteen years of heart failure trials: lessons learned the hard way," Italian Heart Journal, vol. 1, Suppl 3, pp.S108-S109 (2000), that positive inotropic agents, of which compound (I) is a member, "produce striking short-term benefits but increase mortality in patients with left ventricular dysfunction." Kasper at p. S108, 2nd col., 2nd full paragraph. Additionally, one positive inotropic agent, digoxin, neither increased nor changed the mortality of patients when

compared to a control group of patients given a placebo. *Id.* at p. S108, col. 2, 3rd full paragraph.

The review article of Katz, "Heart failure: a hemodynamic disorder complicated by maladaptive proliferative responses," Journal of Cellular and Molecular Medicine, vol. 7, no. 1, pp. 1-10 (2003), also details the results of several long-term clinical trials in which treatments for congestive heart failure, including positive inotropic agents, led to a notable detriment in mortality despite the treatment's initial ability to alleviate the symptoms of congestive heart failure. In particular, "[i]notropic agents, while providing immediate relief of symptoms, generally shorten long-term survival." *Id.* at page 1 in the Abstract; page 1 in the introduction; page 4, cols. 1-2. The observation that positive inotropic agents could initially relieve certain symptoms of congestive heart failure, but increase mortality or leave mortality unchanged, would not have given one skilled in the art a reasonable expectation that compound (I) would successfully decrease mortality as claimed.

Copies of the two articles discussed above are provided in a Supplemental Information Disclosure Statement filed concurrently with this Response.

The mortality reducing effect of compound (I) in congestive heart failure patients was unexpectedly found in the clinical trials conducted by the applicants. The present invention provides a remarkable advantage and breaks the earlier prejudice by providing positive inotropic therapy that not only improves symptoms but also lowers mortality in heart failure patients.

For at least the reasons discussed above, the rejection should be withdrawn.

Additionally, several of the cited references simply disclose a heart contractility enhancing (positive inotropic) effect of compound (I). They do not suggest that mortality of patients suffering from heart failure would be reduced. A skilled person would rather appreciate that positive inotropic agents were known to have detrimental effects on the mortality of heart failure patients, as explained above.

IV. Double Patenting

The Examiner rejected claims 3 and 4 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 10 of U.S. Patent No. 6,949,548 to Poder et al. Applicants do not necessarily agree with this double patenting rejection. Applicants nonetheless enclose a Terminal Disclaimer and accompanying fee that should obviate the rejection. The filing of the Terminal Disclaimer to obviate the rejection does not constitute an admission of the propriety of the rejection. *See* MPEP § 804.02. In view of the above, this rejection should be withdrawn.

In view of the remarks presented above, applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: May 30, 2006

By: _____
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